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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,927	09/17/2003	John C. Prescott	39750-0006 P1	6974

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EXAMINER	
LUNDGREN, JEFFREY S	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 09/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/666,927	PRESCOTT ET AL.	
	Examiner	Art Unit	
	Jeff Lundgren	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) *47-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *see office action*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-46, in the reply filed on May 2, 2006, is acknowledged.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on December 12, 2003, has been considered by the Examiner. The submission is in compliance with the provisions of 37 CFR § 1.97. Enclosed with this Office Action is a return-copy of the Form PTO-1449 with the Examiner's initials and signature indicating those references that have been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-32 and 34 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, and all dependent claims, are indefinite for reciting "capable" in the method claims because it is not clear if this step is being performed (*i.e.*, not a positive, proactive step). Correction is required.

Claim 15 is indefinite for reciting the phrase "without further modification" because it is not clear how this limitation adds to the claim in view of the reactive group (*i.e.*, no distinguishable boundary). Correction is required.

Claim 4 is indefinite for reciting the term "flexible" to describe the linking group because one of ordinary skill in the art would not reasonably be able to determine the metes and bounds of this limitation. For example, it is not clear if the term "flexible" conveys a certain degree of quantifiable motility about a bond axis, or is just a general term where every linker is 'flexible.' Neither the specification or any art of record help to clarify. Correction is required.

Claim 11 is indefinite for reciting the term "locked" because one of ordinary skill in the art would not reasonably be able to determine the metes and bounds of this limitation. For example, this term does not appear to be an art-accepted term, and is not reasonably defined in the specification. Claim 34 is similarly indefinite. Correction is required.

Claim 11 is indefinite for reciting the term "alteration" because one of ordinary skill in the art would not reasonably be able to determine the metes and bounds of this limitation. For example, it is not clear from any related art or Applicants' disclosure what constitutes and "alteration" to the amino acid. Correction is required.

Claims 14 and 34 recite the limitations "the invariant aspartic acid residue in the catalytic loop," "the arginine residue," "the invariant aspartic acid residue in the DFG motif" and "the invariant lysine residue." There is insufficient antecedent basis for these limitations in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-10, 17-28, 31-33, 35-46, are rejected under 35 U.S.C. 103(a)[1] as being unpatentable over Erlanson *et al.* ("Erlanson") "*Site-Directed Ligand Discovery*" *PNAS 19*:9367-9372 (**2000**), in view of Schindler *et al.*, *Science 289*:1938-1942 (**2000**).

The scope and content of the claims are compared to the teachings in Erlanson below:

Claim 1	***Erlanson***
A method for identifying a ligand binding to an inactive conformation of a target protein kinase, comprising:	"We have developed an alternative strategy to rapidly and reliably identify small soluble drug fragments (molecular weight '250 Da) that bind with low affinity to a specifically targeted site on a protein or macromolecule" (p. 9367)
a) contacting the inactive conformation of said target protein kinase, which contains or is modified to contain a reactive group at or near a binding site of interest, with one or more ligand candidates capable of covalently bonding to said reactive group thereby forming a kinase-ligand conjugate; and	"This method relies on the formation of a disulfide bond between the ligand and a cysteine residue in the protein of interest (Fig. 1A)" (p. 9367); the disulfide bond is reversible, such as under a thiol exchange reaction;
b) detecting the formation of said kinase ligand conjugate and identifying the ligand in said kinase-ligand conjugate.	"Tethered compounds can then be identified by MS. Furthermore, the tethered complex is amenable to analysis by x-ray crystallography, which greatly facilitates the optimization of affinity once the disulfide tether is removed." (p. 9367); the molecular weight measurement by MS meets the physicochemical property limitation; "In a typical experiment, 1 ml of a DMSO solution containing a library of 8–15 disulfide containing compounds is added to 49 ml of protein-containing buffer. These compounds are chosen so that each has a unique molecular weight; ideally, these molecular weights differ by at least 10 atomic mass units so that deconvolution is unambiguous. Although we have typically chosen to screen pools of 8–15 disulfide-containing compounds for ease of deconvolution, larger pools can be used as discussed below and as shown in Fig. 2C... ...The identity of any library member bonded through a disulfide bond to the protein is then easily determined by subtracting the known mass of the unmodified protein from the observed mass. (p. 9368)

[1] This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a

Claims 2-4 further limit the method of claim 1 by disulfide bond formation through a thiol, and a flexible linker, as taught by Erlanson (see Figure 1, and description thereof); see also with regard to claims 35 and 36. Claim 5 requires a particular linking group, as taught by Erlanson (Figure 1B); claim 6 further requires a plurality of ligand candidates, as taught by Erlanson (page 9369-9371).

Erlanson teaches using a library in a drug-optimization effort based on a ligand library, *e.g.*, affinity maturation, and recognizes the advantages of identifying significant structure activity relationships for measurable optimization:

> "We have developed an alternative strategy to rapidly and reliably identify small soluble drug *fragments* (molecular weight '250 Da) that bind with low affinity to a specifically targeted site on a protein or macromolecule."

Erlanson, at page 9367, col. 1 (emphasis added). The measurements involving the ligands identifies statistically significant physicochemical properties, i.e., the mass of the bound ligands. Further:

> "After screening a library of 1,200 compounds, *we started to observe some highly significant structure–activity relationships (SAR), as shown in Fig. 3*. [note that in Figure 3, a number of chemical features are shown that are pertinent to the discussion] There is evidently a fair amount of flexibility around the phenyl ring, as shown by the fact that the methyl group can be replaced by a t-butyl group or removed entirely. However, the phenyl-sulfonamide core moiety appears to be essential, because methyl proline is not selected. Furthermore, the proline ring itself appears to be quite important; replacing it with a phenylalanine, phenylglycine, or pyrrole causes the resulting compound not to be selected."

Id., at page 9369, col. 2 (emphasis added). Erlanson further teaches:

> These results demonstrate that the tethering methodology can rapidly identify small low-affinity ligands. However, *to be useful for drug discovery, the ligands identified must be amenable to medicinal chemistry and affinity maturation.* In the case of N-tosyl-D-proline, examination of the bound structures revealed that the tosyl group is in roughly the same position and orientation as the benzamide moiety of methylenetetrahydrofolate, the natural cofactor for this enzyme (17, 21, 22). Given this positioning, *we grafted the glutamate residue* from

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later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

methylenetetrahydrofolate onto the methyl group of N-tosyl-D-proline to try *to enhance the affinity of the molecule* (Fig. 5).

A series of compounds was synthesized and tested for TS inhibition. The *parent compound, in which L-glutamate is grafted onto N-tosyl-D-proline, is almost 50-fold more active than N-tosyl-D-proline alone* (Ki = 24 ± 7 μM). The a-carboxylate of the glutamate residue is very sensitive to modification, in that converting it to a primary amide reduces the affinity by an order of magnitude (not shown). Several substitutions were also incorporated at the proline carboxyl group; in one case, the *displacement of the negatively charged carboxyl group away from the proline ring by two methylene units improves the inhibition constant by more than 70-fold*, to Ki 5 330 6 40 nM (Fig. 5). *Converting this b-alanine appendage to the isosteric isoamyl group* [i.e., converting $2NHCH_2CH_2CO_2H$ to $2NHCH_2CH_2CH(CH3)_2$, not shown] *decreases the binding affinity by more than an order of magnitude (Ki = 12 ± 2.5 μM), suggesting that the displaced carboxylate is critical for improved binding.* The crystallographic structures of TS complexed with two of the improved inhibitors (Table 1 and Fig. 6) reveal that the proline ring and the tosyl group overlap in all three structures, whereas the b-alanine and glutamate appendages make contacts with surrounding protein residues. *The combined effects of these added substituents increase the affinity of one of the inhibitors for TS by more than 3,000-fold over N-tosyl-Dproline. The affinity of this inhibitor is submicromolar and thus well within the range of typical drug leads.*

In this study, we have focused on disulfide tethers. Although it is possible to use other types of reversible bonds, such as imines (23), the disulfide bond is well suited for tethering. Disulfide bonds can be formed and broken under very mild conditions with complete chemoselectivity. Moreover, the disulfide moiety itself can be easily introduced into a wide variety of small molecules at the end of a flexible and variable length tether...

A reasonable extension of the tethering technology would be to discover two weakly binding fragments that bind near one another and to link them to produce higher affinity compounds (27–31). Such a strategy has been applied in the technique ''SAR by NMR'' (32). In many cases, the new linked compounds bind to the target protein with much higher affinity than the precursors (33). Our tethering approach can also rapidly generate candidate molecules for linking.

...In principle, new cysteines can be placed anywhere; for example, if a cysteine is introduced onto the surface of a protein in an area known to be

> important for protein–protein interactions, small molecules could be selected that bind to and block this surface. We expect this covalent tethering methodology to be a powerful technique for generating drug leads.

Id., at page 9370, col. 2 through page 9371, col. 2 (emphasis added). The ligand attachment sites to TS are at or near the active site.

The limitations of claim 7-10 directed to a particular molecular weight, are met by Erlanson (see captioned section above); see also in regard to claims 39-42.

Claims 19 and 20 (and claims 37 and 38) require the formation of a reversible covalent bond in the presence of a reducing agent, and wherein the reducing agent is mercaptoethanol; Eralanson teaches these limitations (see quoted section above; also page 9368, col. 2).

Erlanson teaches characterizing a ligand library with a protein can be applied to the x-ray crystallographic measurement of Erlanson instead of the MS measurement (see page 9370), and also the protein is contacted individually with the library members for x-ray diffraction measurements, as required by claims 21-28 and 43-46. The two ligands of Erlanson bind to non-overlapping sites (see Figure 4 and description thereof) and suggests the synthesis of the joint compound (see Figure 3 and 5, and description thereof), as required by claims 31 and 32.

The limitation of the positional variants, as in claim 7, is met by Erlanson's site-directed cysteine mutagenesis/elimination as shown at positions 143, 146 and/or 147 of TS (see page 9370, columns 1 & 2); the other limitations of claim 7 have been previously addressed above as described in claim 1. The formation of the reversible bond is done in the presence of 2-mercaptoethanol (page 9368, col. 2), *i.e.*, a reducing agent (as in claim 8).

Erlanson does not explicitly teach the use of an inactive kinase.

Schindler discloses the results of an investigation into the physicochemical association between a STI-571 variant and Abelson tyrosine kinase (Abl), a kinase that causes chronic myelogenous leukemia (CML), and reports the crystal structure of the catalytic domain of Abl, complexed to the variant. Schindler teaches that critical to the binding of STI-571 is the adoption by the kinase of an inactive conformation, in which a centrally located "activation loop" is not phosphorylated. The conformation of this loop is distinct from that in active protein kinases, as well as in the inactive form of the closely related Src kinases. Schindler states:

> "These results suggest that compounds that exploit the distinctive inactivation mechanisms of individual protein kinases can achieve both high affinity and high specificity."

Schindler, page 1938, Abstract; and:

> "The ability of the catalytic domains of protein kinases to adopt characteristic inactive conformations is proving to be a hallmark of these proteins. That STI-571 takes advantage of this feature of its target is encouraging news for the further development of specific protein kinase inhibitors."

Schindler, page 1941, col. 1, last paragraph.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention because the art relates to the teaching of Schingler. Schindler, who discloses the results of a crystallographic investigation of a certain inhibitor and an inactive kinase, teaches how inactivated kinases represent a desirable target for therapeutic action and future drug development. Each of Erlanson and Schindler are directed to studying the inhibition of biologically active molecules; Erlanson is predominantly is focused on the combinatorial chemistry used to exploit certain target kinases, whereas Schindler is focused on the particular target of the inactive kinase. One of ordinary skill in the art would have been motivated to select the inactivated kinase as the target biological molecule and approach of Erlanson with the in the inactive state as taught by Schindler because of the increased affinity and specificity. Therefore, the invention as a whole was prima facie obvious at the time it was invented.

Claims 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Erlanson and Schindler, as applied to claims 1-10, 17-28, 31-33, 35-46 above, and further in view of Roben *et al.*, U.S. Patent No. 6,903,196.

The limitations of claims 1-10, 17-28, 31-33, 35-46 and the applicable teachings of Erlanson and Schindler are set forth above, and hereby incorporated by reference.

Neither Erlanson or Schindler explicitly disclose capillary electrophoresis or high performance liquid chromatography.

Roben teaches that This invention provides novel methods of and kits for labeling and isolating lumen-exposed molecules, particularly polypeptides which are expressed in a tissue-specific or organ-specific manner. The methods and kits can be used to isolate molecules exposed on the luminal side of cells lining vascular, ductal, sinus, respiratory, fascial, and other perfusible tissue spaces. Certain of the mass-sensitive detection methods disclosed by Roben include the detection of isolate molecules (e.g., organ- or tissue-specific polypeptides) exposed on a luminal surface of a perfusible space. These molecules, such as polypeptides, and the like can be analyzed and quantified by any of a number of general means well known to those of skill in the art, including electrospray ionization (e.g., Fourier transform ion cyclotron resonance mass spectrometry; see, e.g., U.S. Pat. No. 6,011,260), radiography, electrophoresis, capillary electrophoresis, high performance liquid chromatography (HPLC).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Erlanson, Schindler and Roben are directed to the detection and analysis of chemically modified proteins/peptides by mass-sensitive methods. One of ordinary skill in the art would recognize the advantages of chromatographic separation techniques, such as improved detection and resolution of the desired target. Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claims because the examined application claim is either anticipated by, or would have been obvious over, the reference claims. See, *e.g.*, In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10, 17-28, 31-33 and 35-46, are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, of U.S. Patent No. 6,919,178 B1 ("the '178 patent," issued to Erlanson *et al.*, on July 19, 2005), in view of Schindler *et al.*, Science 289:1938-1942 (2000), or alternatively a provisional rejection over claims 1-16 of U.S. Patent Application No. 10/394,322.

The courts have clearly conveyed that a later genus claim limitation is anticipated by, and therefore not patentably distinct from, an earlier species claim. In re Berg, 140 F.3d at 1437, 46 USPQ2d at 1233 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 1053, 29 USPQ2d 2010, 2016 (Fed. Cir. 1993); In re Gosteli, 872 F.2d 1008, 1010, 10 USPQ2d 1614, 1616 (Fed. Cir. 1989); Titanium Metals Corp. v. Banner, 778 F.2d 775, 782, 227 USPQ 773, 779 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d at 944, 214 USPQ at 767 (C.C.P.A. 1982).

Compare the generic claim 1 and 33 of the instant application to the following:

U.S. Application No. 10/394,322 (Claim 59)	*the '178 patent (Claim 1)*
A method for identifying ligands binding to an inactive conformation of a target protein kinase, comprising	A process comprising the steps of:

U.S. Application No. 10/394,322 (Claim 59)	*the '178 patent (Claim 1)*
(a) contacting the inactive conformation of said protein kinase having a first and a second binding site of interest and containing or modified to contain a nucleophile at or near the first site of interest with a plurality with a plurality of ligand candidates, said candidates having a function group reactive with the nucleophile, under conditions that a reversible covalent bond is formed, between the nucleophile and a candidate that has affinity for the first site of interest, to form a kinase-first ligand complex;	(i) contacting a Target Biological Molecule (TBM) having a first and a second site of interest, and containing or modified to contain a nucleophile, selected from the group consisting of thiol, protected thiol, reversible disulfide, hydroxyl, protected hydroxyl, amino, protected amino, carboxyl and protected carboxyl groups, at or near the first site of interest, with a plurality of first organic ligand candidates, said candidates having a functional group reactive with the nucleophile, under conditions such that a reversible covalent bond is formed between the nucleophile and a candidate that has affinity for the first site of interest, to form a TMB-first ligand complex;
(b) identifying the first ligand from the complex of (a);	(ii) identifying the first ligand from the TBM-first ligand complex;
(c) designing a derivative of the first ligand identified in (a) to provide a small molecule extender (SME) having a first functional group reactive with the nucleophile on the kinase and a second functional group reactive with a second ligand having affinity for the binding second site of interest;	(iii) designing a derivative of the first ligand identified in (ii) to provide a small molecule extender (SME) having a first functional group reactive with the nucleophile on the TBM and a second functional group reactive with a second ligand having affinity for the second site of interest, wherein said first functional group is capable of forming an irreversible covalent group with the thiol, protected thiol, reversible disulfide bond, hydroxyl, protected hydroxyl, amino, protected amino, carboxyl or protected carboxyl group on said TBM;
(d) contacting the SME with the kinase to form a kinase-SME complex, and	(iv) contacting the SME with the TBM to form a TBM-SME complex, and
(e) contacting the kinase-SME complex with a plurality of second ligand candidates, said candidates having a functional group reactive with the SME in said kinase-SME complex, wherein a candidate that has affinity for said second binding site of interest on said kinase forms a reversible covalent bond with said kinase-SME complex, whereby a second ligand is identified	(v) contacting the TBM-SME complex with a plurality of second small organic ligand candidates, said candidates having a functional group reactive with the SME in said TBM-SME complex, wherein a candidate that has affinity for said second site of interest on said TBM forms a reversible covalent bond with said TBM-SME complex, whereby a second ligand is identified.

The teachings of Eralnson and Schindler, as well as the detailed scope of the instant claims are incorporated by reference from the rejection above.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention because the differences between the instant claims and that of claims in the '178 patent of the '322 application is the selection of a specific target biological molecule, namely, an inactive kinases. Claim 1 of the '178 patent captures the claimed tethering method for screening for inhibitor compounds against any TMB, including kinases. Schindler,

who discloses the results of a crystallographic investigation of a certain inhibitor and an inactive kinase, teaches how inactivated kinases represent a desirable target for therapeutic action and future drug development. Each of the '178 patent and Schindler are directed to studying the inhibition of biologically active molecules; the '178 patent predominantly is focused on the combinatorial chemistry used to exploit certain targets, whereas Schindler is focused on the particular target of the inactive kinase. One of ordinary skill in the art would have been motivated to select the inactivated kinase as the target biological molecule of claim 1 of the '178 patent because of the advantages of maintaining the kinase in the inactive state as taught by Schindler. Accordingly, claims 59, 60 and 76, of the instant application are prima facie obvious over the art of record.

Conclusions

No claim is allowable.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JSL

My-Chau Tran
Patent Examiner